amic and pituitary hormone release. AEDs change levels of pituitary and gonadal hormones involved in sexual behavior by altering metabolism and protein binding and probably also through direct effects on the hypothalamic-pituitary axis. Women with sexual dysfunction should undergo an endocrine evaluation (thyroid hormones, estrogen, testosterone, and prolactin), psychological evaluation, and referral to a gynecologist. Changing to another AED is sometimes helpful.

Pregnancy raises several concerns for woman with epilepsy, including the risk of more frequent maternal seizures, of pregnancy complications, and of birth defects. Fortunately, a better understanding of the risks associated with pregnancy in the epileptic patient has led to treatment strategies to optimize outcome.

About 25% to 30% of women with epilepsy have more frequent seizures during pregnancy, while a similar number find that seizures are less frequent. Poor seizure control may be related to lower total levels of AED. To a lesser extent, the non–protein bound fraction of AED may be decreased as well. Women with epilepsy also have more pregnancy complications such as vaginal bleeding and abruptio placentae, and there is a two-fold increase in the incidence of adverse pregnancy outcomes, including fetal wastage and neonatal and perinatal death.

AED use during pregnancy is associated with a higher risk of fetal malformation. The risk of congenital malformation, such as cleft lip or palate and ventricular septal defect, is 4% to 8% in infants of mothers with epilepsy who are exposed to any AED, compared to 2% to 4% of infants born to women without epilepsy. There is a 1% to 2% incidence of neural tube defects in fetuses exposed to valproic acid during the first trimester, and a 0.5% to 1% risk after exposure to carbamazepine. Congenital anomalies, mostly involving the mid-face and digits, occur in between 5% to 30% of infants exposed to AEDs. AED-associated teratogenesis may occur because of fetal exposure to toxic free-radical AED intermediates. Particularly susceptible people are those with deficiencies in free-radical metabolizing enzymes. Malformations may also occur as a result of AED-related folate deficiency.

Specific treatment strategies can significantly reduce these risks. Treatment with folate before conception and during pregnancy substantially reduces the risk of neural tube defects in nonepileptic women who are at risk and is thought to confer the same protective action in women with epilepsy. The optimal dose is not established but appears to be between 0.4 mg and 4 mg per day. Indicated prenatal diagnostic testing for women with epilepsy includes high resolution ultrasound and maternal serum alpha-fetoprotein obtained between 16 and 18 weeks gestation; neural tube defects will be detected with greater than 95% sensitivity. Vitamin K is administered during the final month of pregnancy as oral Vitamin K1 (phytonadione, 10 mg per day) to prevent AED-associated fetal and maternal coagulopathy. Adverse outcomes are minimized by treating with AED monotherapy, rather than polytherapy, and by using the lowest effective AED dose. Monitoring the non–protein bound fraction of AED is most accurate during gestation.

The new AEDS (felbamate, gabapentin, lamotrigine, tiagabine, topiramate) have limited human pregnancy experience, but these drugs have not been teratogenic in animals. A prospective AED pregnancy registry has been established by an independent scientific advisory group and financed by five pharmaceutical companies manufacturing AEDs. Women who become pregnant while receiving any AED should be encouraged to enroll with the registry (contact information is provided below).

Epilepsy is a chronic illness that affects women during the child-bearing years. The expression of epilepsy may be altered with physiological changes in ovarian steroid hormones and as a consequence of exposure to therapeutic steroid hormones. Fertility may be reduced because of alterations in the hypothalamic pituitary-gonadal axis, in gonadal steroid concentrations, and in ovarian morphology. Sexual dysfunction may present as specific physiological complaints. Pregnancy and fetal outcome can be maximized by maintaining seizure control, utilizing AED monotherapy, and reducing peak-dose exposure. Routine folic acid supplementation appears prudent for any woman of child-bearing potential on AEDs. Further information is available for health care professionals and consumers through the Epilepsy Foundation.

The Antiepileptic Drug Pregnancy Registry
Genetics and Teratology Unit
14CNY-MGH East
Room 5022A
Charlestown, MA 02129-2000
1-888-233-2334
website: neuro-www2.mgh.harvard.edu/aed/registry.nclk

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4351 Garden City Drive
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## New Pharmacological and Surgical Therapies for Parkinson's Disease

REPLACEMENT THERAPY WITH dopamine precursors (levodopa) or dopamine agonists remains the mainstay of symptomatic therapy for Parkinson's disease. Two new selective dopamine D-2 and D-3 receptor agonists, pramipexole and ropinirole, are now available. Both are

being used as initial treatment for symptomatic Parkinson's disease and can delay the need for levodopa by one or more years. As monotherapy, pramipexole and ropinirole are largely devoid of the adverse effects that frequently complicate treatment with levodopa, namely motor fluctuations (in the most severe form known as "on-off") and dyskinesia (involuntary choreic movements). Pramipexole and ropinirole are also used with levodopa in more advanced patients to prolong the response to each dose of levodopa and to reduce the trough severity of parkinsonism. Both new agonists are well tolerated but can have adverse effects that resemble those of other dopaminergic agents, such as nausea, dizziness, orthostatic hypotension, confusion, and hallucinations. In conjunction with levodopa, they can cause dyskinesia. Because pramipexole and ropinirole are not ergot derivatives, they may lack rare adverse effects such as retroperitoneal and pulmonary fibrosis associated with the older dopamine agonists. Direct comparisons among the new and old dopamine agonists are scant, but some studies suggest that ropinirole and pramipexole may be superior to bromocriptine.

Tolcapone and entacapone, inhibitors of catechol-O-methyl transferase (COMT), will be introduced in the near future; Tolcapone is FDA approved. These drugs block O-methylation of levodopa to an inert compound, thereby slowing clearance of levodopa from plasma and increasing the amount of levodopa entering the brain, which enhances the response to levodopa. Their effect is somewhat like controlled-release levodopa. The COMT inhibitors have no clinical effect unless they are combined with levodopa. The side effects of tolcapone and entacapone alone are diarrhea. In combination with levodopa, the adverse effects are the same as those of excessive levodopa, so it is often necessary to reduce the levodopa dose.

Protective therapies to slow the degeneration of dopaminergic neurons remain at the forefront of scientists' and clinicians' minds. Selegiline, a selective, irreversible MAO-B inhibitor, was widely adopted following the Parkinson's Study Group report that it delayed the need to start levodopa by over a year. The initial enthusiasm for selegiline has been tempered by the recognition that selegiline can reduce or reverse symptoms but not necessarily affect the progression of the disease. So although selegiline's symptomatic actions can contribute to the delay in need for levodopa, it does not clearly alter progression of the disease once levodopa is started. A large British study suggested that selegiline increased mortality rates, but this finding has not been replicated. Thus, the protective actions of selegiline are controversial. In current clinical practice, selegiline is more commonly used in patients early in the disease and withdrawn later in the course when patients are on multiple antiparkinsonian drugs. It can cause confusion, dyskinesia, orthostatic hypotension, and nausea. Despite the uncertainties that surround selegiline, the search for protective therapies continues with investigations of agents to reduce free-radical formation and damage in the basal ganglia, of glutamate antagonists to reduce excitotoxicity, and of mitochondrial electron chain cofactors to enhance neuronal energy production.

Thalamotomy is increasingly used for disabling rest or postural tremor that is unresponsive to pharmacological management. Unilateral thalamotomies abolish or greatly reduce contralateral tremor but do not affect the other parkinsonian signs of rigidity and bradykinesia. Bilateral procedures are associated with a high incidence of dysarthria, dysphagia, and disequilibrium, and they are only reluctantly used in severely affected patients. A new approach is to implant stimulating electrodes in the thalamus, because high-frequency stimulation will inactivate neurons in the vicinity of the electrode tip and produce a reversible thalamotomy. Adverse effects can be minimized by altering the stimulation parameters, and bilateral procedures can be done without the concern of irreversible dysarthria, dysphagia, and disequilibrium. The drawbacks are the expense of the stimulator, the periodic need for battery replacement, and the considerable effort required to find the optimal stimulation parameters. A common compromise is to do a thalamotomy on the first side and, if needed, thalamic stimulation on the contralateral side at a later date. Pallidotomy ameliorates contralateral levodopa-induced dyskinesia. It may also improve other aspects of parkinsonism, but severe dyskinesia is the major indication for the procedure. The adverse effects of bilateral pallidotomies are similar to those of bilateral thalamotomies and are therefore rarely performed. Unilateral and bilateral stimulation of the pallidum and subthalamic nucleus are promising, safer techniques that are under intense investigation for treatment of parkinsonism.

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## Recent Advances in the Treatment of Neuropathies

THERE IS A GROWING arsenal of immunomodulating therapies—including glucocorticoids, immunosuppressant drugs, intravenous immune globulin (IVIg), and plasmapheresis—that is used to treat peripheral neuropathies. These therapies control underlying immune processes that attack nerves. Recovery from dysimmune neuropathies, however, requires more than the control of underlying immune processes. It also requires repair and recovery of peripheral nerve that no therapy has been shown to enhance or alter. In axonal neuropathies, the goal is stabilization of function, because recovery follows axon regeneration and collateral reinnervation. This takes years and is incomplete. In demyelinating